Dynamic susceptibility contrast perfusion MRI: concepts and applications

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Introduction

Since the early studies in the late 1980s, *dynamic susceptibility contrast MRI* (DSC-MRI, also known as '*bolus tracking*') has become a very powerful technique for the assessment of perfusion[1], and perfusion-related parameters (see (1,2) for recent reviews). Despite the need of an exogenous MR agent (cf. arterial spin labeling techniques), DSC-MRI is currently the *most common MR perfusion methodology in clinical studies*. This is due to the relatively high signal changes introduced by the contrast agent, the short acquisition time required, and the wealth of information that generates (it provides information not only about CBF but also about other hemodynamic parameters within the same scan). It relies on the injection of a *bolus of a paramagnetic contrast agent*, which produces a transient decrease in signal intensity on a series of *gradient-echo or spin-echo images* acquired during its passage through the brain (3). The loss in signal intensity is due to the decrease in T_2* or T_2 associated with the susceptibility-induced gradients surrounding the paramagnetic contrast agent (4). This effect is more significant in areas where the contrast agent is compartmentalized (since this increases the induced gradients) and makes quantification of cerebral perfusion in areas with blood-brain barrier (BBB) leakage more complex (see later). Since the passage of the bolus through brain tissue is of the order of a few seconds, a *very fast imaging method is required* to fully characterize the induced signal changes. The most common imaging technique currently used is EPI, which allows for a good compromise between time resolution (typical TR≈1.5sec), image coverage (typically 10-15 slices) and spatial resolution (typical voxel size 2x2x5mm^3).

Quantification – Convolution

The changes in relaxation rate ΔR_2* are related to the contrast agent concentration: the larger the concentration, the larger the observed effect. Early work has suggested that this *relationship* can be *assumed to be linear* (3-5):[2]

$$C(t) = k \cdot \Delta R_2^*(t) \tag{1}$$

where $C(t)$ is the time dependent contrast concentration, and k is a proportionality constant that depends on the tissue type, the contrast agent, the field strength, and the pulse sequence. Therefore, if *one assumes negligible T1 effects* during the bolus passage, $C(t)$ can be calculated from the changes in signal intensity with respect to its baseline (i.e. pre-injection) value:

$$C(t) = -\frac{k}{TE} \cdot Ln\left(\frac{S(t)}{S_0}\right) \tag{2}$$

where $S(t)$ is the signal intensity at time t, S_0 is its baseline value, and TE the echo-time of the MR sequence.

The concentration in the tissue is not only proportional to CBF, but it is also affected by how the study is done (for example, a slower injection will lead to a wider $C(t)$). Using indicator dilution theory, the concentration time course can be shown to be expressed by a *convolution* equation (9,10):

$$C(t) = \alpha \cdot CBF\left(C_a(t) \otimes R(t)\right) = \alpha \cdot CBF \int_0^t C_a(\tau) R(t-\tau) d\tau \tag{3}$$

where the symbol $\otimes$ indicates the convolution operation, $C_a(t)$ is the *arterial input function* (AIF), i.e. the function describing the contrast agent input to the tissue of interest, and $R(t-\tau)$ is the tissue *residue function*, which describes

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[1] Throughout this document the terms *perfusion*, *cerebral blood flow* (and its acronym *CBF*) will be used indistinguishable.

[2] Although a linear relationship is usually used, recent studies have suggested that this *linear relationship may not always be valid*, particularly for large contrast concentration such as in big vessels (6,7). Therefore, although the assumption of a linear relationship may be valid for the concentration in the tissue, it may be a significant source of error in the measurement of the arterial input function (see later). Possible solution: use the phase information of the MR images (7,8).

the fraction of contrast agent remaining in the tissue at time *t*, following the injection of an ideal instantaneous bolus at time τ. The proportionality constant α depends on the density of brain tissue, and the difference in hematocrit levels between capillaries and large vessels (to compensate for the fact that only the plasma volume is accessible to the contrast agent) (1). The integral in Eq.(3), accounts for the fact that for a non-ideal bolus, part of the spread in the concentration time curve is due to the finite length of the actual bolus. It is possible to interpret the integral expression in Eq.(3) by considering the AIF as a superposition of consecutive ideal boluses "$C_a(\tau)d\tau$" injected at time τ. For each ideal bolus, based on the definition of the residue function, the concentration still present in the tissue at time *t* will be proportional to "$C_a(\tau)R(t-\tau)d\tau$", and the total concentration $C_t(t)$ will be given by the sum (or integral) of all these contributions.

Quantification – *De*convolution

Quantification of CBF therefore involves inversion of Eq.(3), a mathematical process known as *deconvolution* (10). This *requires measurement of the AIF* (see later), and calculating the scaled residue function $CBF \cdot R(t)$ (known as the impulse response function). Once this function is calculated, perfusion can be obtained from its initial (or maximum) value, since $R(t=0)=1$ by definition. Although inverting Eq.(3) (i.e. performing the deconvolution) may appear simple at first sight, this inverse problem is known mathematically as an *ill-posed problem*. This means that even a tiny amount of noise in the measured concentration curves will have huge effect on the calculated impulse response (and thus CBF!). Therefore, a considerable amount of work has been done in the last decade to develop, assess, and compare various deconvolution algorithms. Some of the algorithm proposed to date include: Fourier Transform approach (10,11), singular value decomposition (SVD) and its variants (10,12,13), maximum-likelihood maximization (14), Tikhonov regularization (15), expansion in orthogonal polynomials (16), and Gaussian processes deconvolution (17). Ideally an algorithm should lead to accurate measurements under a wide a range of practical situations, such as under various tissue characteristics (e.g. perfusion values, residue function models), imaging characteristics (e.g. SNR levels), sequence parameters (e.g. TR, TE), as well as for other experimental conditions (such as the presence of bolus delay to areas with abnormal vascular supply). Furthermore, the algorithm should be fast to be able to be used in a clinical environment. Unfortunately, there is currently no single algorithm that fulfils all these requirements; the likely reason for the lack of consensus between users. It is for this reason that this is still an area of very active research.

Quantification – CBV and MTT

DSC-MRI can provide information not only about perfusion but also about other physiological parameters. For example, due to the compartmentalization of the contrast agent within the intravascular space (for an intact BBB)[3], the *cerebral blood volume* (*CBV*) is proportional to the normalized total amount of tracer (i.e. the 'area under the peak') (1):

$$CBV = \alpha^{-1} \frac{\int C_t(t)dt}{\int C_a(t)dt} \qquad (4)$$

where the proportionality factor α^{-1} is the inverse of the factor in Eq.(3). The normalization to the integral of AIF accounts for the fact that, the more tracer is injected the greater concentration will reach the tissue, regardless of the CBV. A third physiological parameter accessible by DSC-MRI is the *mean transit time* (*MTT*: the average time for a molecule of contrast agent to pass through the tissue vasculature following an ideal instantaneous bolus injection). These three physiological parameters are not independent, but they are related through the *central volume theorem* (1): MTT=CBV/CBF.

Quantification – Absolute units

DSC-MRI can provide, in principle, CBF in *absolute units* (typically ml/100g/min). There are three main approaches to achieve this:

[3] When the BBB is not intact, quantification of CBV is more complicated; its calculation must account for the contrast agent in the extravascular space (see later).

1. *Use of an internal standard*: since CBF measurements using PET have initially suggested a relatively age-independent and uniform white matter value of 22 ml/100g/min in normal adults, a region in normal white matter was proposed as an internal standard to convert the MR measurement to absolute units (18).
2. *Knowledge of the proportionality constants*: if the values of the constants appearing in the equations above are known, the deconvolution method would lead to absolute measurements (11,19-21).
3. *Use of a scaling factor obtained from a cross-calibration study*: the MR CBF values can be converted to absolute units by using an empirical conversion factor calculated (usually from a separate study) by cross-calibration of DSC-MRI to a 'gold standard' technique (e.g. PET) (22,23).

Although all these approaches have been used to calculate perfusion in absolute units and the values obtained in normal subjects are consistent with expected CBF values, *there are still some concerns* regarding the accuracy under various physiological conditions (24-27), and the agreement might have been fortuitous. In principle, all the approaches can potentially lead to errors, particularly in the presence of pathology. For example, a recent study has shown a wide variability in white matter CBF values measured with PET on the contralateral hemisphere in patients with chronic carotid occlusion (28). Similarly, some studies have shown that the constant k in Eq.(1) may vary between tissue types, subjects, as well as between tissue and arteries (6,29). Furthermore, changes in hematocrit levels (and therefore α) during pathology have been reported (30,31). Similarly, the validity of a single conversion factor under various physiological conditions remains to be shown (27,28,32). Therefore, absolute CBF measurements in the presence of pathology should be interpreted with caution. Work is currently under way to address many of these issues, and accurate absolute CBF measurements may be possible in the near future.

Measurement of the AIF

The AIF represents the concentration of tracer entering the tissue at time t. Although this function can vary throughout the slice, its shape is commonly estimated from a major artery (e.g. the internal carotid artery, or the middle cerebral artery), and used as a *global AIF* for all the slices. However, the presence of steno-occlusive disease in an artery may cause distortion of the concentration-time curve between the artery and the tissue of interest as a result of the abnormal flow pattern (25). These distortions can introduce considerable errors in the quantification of CBF (33,34), which can have important implications for the diagnosis and management of patients with cerebral ischemia (25,35). Various deconvolution algorithms have been shown to be insensitive to the presence of delay (see for example (11,13,14), and their use is highly advisable. On the other hand, the *errors due to bolus dispersion* are not related to the particular deconvolution algorithm used, but they are a *more fundamental limitation of the model* used in Eq.(3); this equation assumes that the *true* AIF is measured, and the unaccounted dispersion will be then assigned to occurring within the tissue of interest (i.e. interpreted as a prolonged MTT and decreased CBF (35)). Therefore, it should be noted that while the particular choice of deconvolution algorithm can remove the delay-related errors, it cannot eliminate those associated to bolus dispersion.

To minimize the errors related to bolus dispersion, it has been proposed that a *local AIF* should be used instead (37-38). This requires the estimation of the AIF from an artery as close as possible to the tissue of interest. In fact, by definition, the AIF should be measured on a pixel-by-pixel basis, and a local AIF should be used for the deconvolution in each voxel. This approach is likely to be particularly sensitive to partial volume effects, and various methods to define a local AIF have been proposed. Although further work is required to validate these approaches, they may prove to be a promising solution to *minimizing the dispersion-related errors* in certain group of patients, such as those with arterial stenosis or occlusion.

Quantification – BBB breakdown

The kinetic model described in Eq.(3) is based on the assumption that the contrast agent remains intravascular. If this not the case (e.g. when the *BBB is disrupted*), the distribution of the contrast agent outside the vascular compartment *decreases the T2* effects*, as well as *increases the T1 effects* (usually neglected) during the passage of the bolus. If these effects are not minimized (39) or taken into account (40), significant errors can be introduced in quantification of DSC-MRI data (see (41) for a recent review). In order to account for the T_1 effects, Weisskoff et al (42) *modeled the MR signal in terms of the combined T1 and T2* contributions*. In such a way, they proposed a method to quantify CBV in the presence of contrast leakage, as well as an estimation of vascular permeability (42,43). More recently, this work has been extended to quantify not only CBV and a measure of permeability, but

also CBF (40,44). Since the effects of contrast leakage are included, it should provide a more accurate estimation of perfusion when the BBB is disrupted, although a full validation of these modified models remains to be done.

Applications – Acute stroke

The main application by far has been in *cerebral ischemia*, particularly in the context of acute *stroke* (see (39,45) for recent reviews). The concept of '*diffusion-perfusion mismatch*' (area with an abnormality observed on DSC-MRI but with normal appearing MR diffusion properties) has received great interest in the last decade. Several studies reported the expansion of the initial lesion seen on diffusion imaging, such that the final infarct included tissue that was in the diffusion-perfusion mismatch area during the hyperacute stage. It was initially believed that the mismatch area could therefore be used to identify the ischemic *penumbra* (tissue with preserved neuronal integrity but hypoperfused at a level to cause functional impairment). However, many studies have now shown that not all the mismatch area corresponds to penumbra (46): some of the mismatch can represent tissue areas with *benign oligemia* (areas with normal or slightly decreased perfusion that will survive independently of treatment effects) (47).[4] To improve the tissue characterization during the hyperacute stage, it is now becoming apparent that none of the DSC-MRI maps in isolation will be robust enough to identify the tissue at risk of infarction with sufficient sensitivity and specificity. In the last few years, many groups have been developing *predictor models of tissue infarction* by combining all the available information: the maps obtained using DSC-MRI are used, in combination with diffusion- and T_2-weighted images, in models to predict the fate of the tissue in acute stroke (e.g. see (48-51)), with the final aim of identifying the patients that are more likely to benefit from therapy. This is an area of very active research at present, and a comparison of the various models on a common dataset could prove very useful.

Applications – Chronic ischemia

The areas of mismatch have been observed not only during acute stroke, but also in patients with chronic hypoperfusion. These included patients with internal carotid stenosis or occlusion (16,27,28,52,53), as well as children with high stroke incidence such as those with sickle cell disease (54) and moyamoya syndrome (55). Extensive areas of decreased perfusion (in many cases with normal structural and diffusion imaging (54,55) have been reported. These studies suggest that areas of decreased perfusion can persist for long periods of time, although it is not clear how long such compromised tissue could survive, since the flow "thresholds" for energy failure are expected to increase with time. However, it should be noted that due to the vascular abnormalities present in many of these patients, a significant part of the mismatch area could be associated to errors due to bolus delay and dispersion (25,46).

Applications – Treatment assessment

The use of DSC-MRI has a potential role not only in the identification of tissue at risk of infarction, but also in monitoring the efficacy of interventional strategies. For example, to determine the presence and extent of recanalization (either spontaneous or due to thrombolysis) (56,57), to evaluate the effect of blood transfusion therapy on brain perfusion in patients with sickle cell disease (54), and to assess the effectiveness of surgical revascularisation in moyamoya syndrome (55).

Applications – Cerebrovascular reserve capacity

Perfusion MRI can provide information not only about the "resting" tissue perfusion status, but also about the cerebrovascular reserve capacity. It has been suggested that measurements of regional cerebrovascular reactivity in response to carbon-dioxide, breath holding or acetazolamide could potentially identify the subgroup of patients with carotid artery stenosis or occlusion who may be at increased risk of stroke (58). Perfusion MRI provides a non-invasive means to obtain such information, with good spatial resolution, by comparing the measurement before to that after the vasodilatory stimulus (see for example, (16,32,52)).[5]

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[4] In many cases, the misclassification of oligemia as penumbra can be due to the errors introduced by delay and dispersion: these distortions in the bolus have been shown to introduce CBF and MTT errors (33), which could be misinterpreted as severe hypoperfusion, with potentially serious clinical consequences for patient management (25).

[5] It should be noted that studies of cerebrovascular reserve require repeated injections of contrast agent in DSC-MRI. To avoid the residual effects of the first bolus during the second study, it is advisable to inject a small pre-dose of contrast agent a few minutes before the first study (39).

Applications – Tumors

Due to the complexities of quantifying CBF in the presence of BBB leakage, the majority of the DSC-MRI studies so far have focused on measuring CBV and a permeability index. These applications included use of DSC-MRI for tumor grading, for determining its extent, for the differential diagnosis of recurrence vs. radiation necrosis, and for guiding tumor biopsy (see (59-61) for recent reviews). However, there have been some studies which used the modified (to include leakage) indicator dilution theory (40,44), and quantified also CBF by deconvolution.

Conclusion

DSC-MRI is a very powerful technique that provides unique information regarding cerebral hemodynamics. It has been extensively used for the assessment and management of patients, as well as being an invaluable tool in experimental studies. The principles of measuring perfusion using DSC-MRI have been reviewed, and the main assumptions and steps required for CBF quantification described. The main limitations and artifacts that can affect the accuracy of CBF quantification have been discussed, and the main areas of application were reviewed.

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